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09/730,214	12/05/2000	Jonathan Miller	13993	9173

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EXAMINER	
BORIN, MICHAEL L	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/730,214	MILLER ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-26,28,29,31-33 and 35-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26,28,29,31-33,35-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 22-26,28,29,31-33,35-40 are pending.

2. Rejections not reiterated from previous Office actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112, first paragraph (written description)

3. Claims 22-26,28,29,31-33,35-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 22 is amended to introduce new matter as it recites the following terms (underlined):

- designing proteins which have "previously unknown", "realizable" backbone configurations.
- generating configurations of "preselected length"
- ultimately be inserted in the configuration
- selecting configurations which are both in ground state and novel;
- selecting novel sequences of amino acids

None of the terms underlined above are described, either directly, or implicitly, in the specification. The specification does not address configurations identified by the

instant method as "novel", or "previously unknown", even though it states that the configurations identified by the claimed method can be used in the design of novel compounds. Further, with respect to the term "preselected", specification does not disclose any selection of backbone of any particular length; rather, specification teaches that "a small set of phi-phi angle pairs is used to generate a discrete set of backbone configurations". With respect to the term "ultimately be inserted in the configurations", specification does not teach that amino acids will be inserted into configurations.

4. Examiner further maintains rejection of claims 22-26,28,29,31-33,35-40 under 35 U.S.C. 112, first paragraph, as introducing new matter by using terms

- ...or another space filling generic side chain
- ...evaluating the surface exposure ...of generic side chain

Applicant submits that use of any other nonspherical shape will be obvious for an artisan. The issue, however, is that specification does not disclose any genus of space-fillers – which is being now introduced into the claims - it discloses any "spheres" and nothing else. Thus, reciting "space filling generic side chain" remains to be considered as new matter.

Claim Rejections - 35 USC § 112, second paragraph.

5. Claims 22-26,28,29,31-33,35-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to previously applied rejections, In view of applicant's arguments and applicant's comments in the course of the interview, majority of rejections made under 35 U.S.C. 112, second paragraph, are withdrawn. The following two rejections remain.

C. Claim 1, "evaluating" step: it is not clear how to evaluate "surface exposure of generic side chain" or "surface exposure of a sphere". The specification addresses total surface exposure (p. 9), but does not address surface exposure of the recited model moieties. Even if there had been "real" amino acid residues, no condition under which surface exposure is to be estimated (e.g., type of environment, pH, etc.) are addressed.

Applicant does not provide convincing argument to this rejection. p. 15, last full paragraph states: "Similarly, then, one would apply the same method for evaluating surface exposure of a sphere...". It is not clear, "similarly" to what issue addressed in the in the previous part of response the "evaluating" is to be made: – none of previous arguments addressed evaluating of surface exposure. Even if the description for surface exposure of spheres had been described, it does not explain how is evaluation for more generic "generic side chains" is to be done.

6. The following new ground of rejection is applied in view of amendments to claim 22:

Claims 22-26,28,29,31-33,35-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is amended to recite the step of selecting configurations that are both ground states AND novel. It is not clear how to determine whether a configuration is novel, both for the reason that no criteria for such selection is provided in the specification, and because it is not clear what is being considered to be "novel", as "novel" is a relative term which at any given point of time will be different.

Further, the last step of the amended claim 22 addresses selecting "novel sequences of amino acids". It is not clear how to select said sequences of amino acids . It is not clear, what represents "novel" with regard to said sequences, as the term "novel" is a relative term which at any given point of time will be different. It is not clear which "one of the selected configurations" is to be picked for selecting the "novel sequences of amino acids". Further, it is not clear whether the amino acid residues are

supposed to "adopt" one of selected configurations as stated at the end of the claim, or to be "inserted" into the backbone as addressed in the "assigning step".

Claim Rejections - 35 U.S.C. § 101 (utility)/ 112-1

7. Claims 22-26,28,29,31-33,35-40 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility due to its not being supported by a substantial utility or a well established utility.

The invention is drawn to method for designing proteins by a computational method which includes steps of generating a protein backbone populated with model spheres or space-filling generic side chains, generating sequences of randomly generated hydrophobicities, identifying highly designable configurations which have not been described and selecting novel sequence of amino acids which can adopt one of the selected novel configurations.. The claims do not recite any steps of preparing particular proteins of interest, are not directed to determining designability of proteins related to any natural proteins of interest. An *in silico* method to design proteins for a particular activity would have a patentable utility. However, as set forth above, the instant claims do not recite design of any particular protein.

The Court of Customs and Patent Appeals has stated:
"Practical utility is a shorthand way of attributing "real-world" value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public."

A "use" to do further research is not considered a utility which provides an "immediate benefit" to the public.

Examples of situations requiring further research to identify or reasonably confirm a "real world" context of use, and which do not have utility under 35 USC 101, as set forth in MPEP 2107.01.1, include:

(A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved',
and
(C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility.

Applicant argues that "the utility of the claimed invention is as a means of applying the powerful computational tools available today to test myriad combinations of backbone configurations and amino acid sequences and to thereby determine novel structures that have potential "real world" application." Examiner agrees that the method produces some amino acid sequences, but disagrees in regard to immediately recognizable "real world" use of these arbitrary sequences. This is because the method is not directed to any particular protein of interest, but rather is aimed at modeling protein backbone populated with model spheres or space-filling generic side chains and generating sequences of randomly generated hydrophobicities for which low energy state configuration in being determined. All the method achieves is bending a model peptide backbone into certain configuration using arbitrary set of angles and then determining which amino acid residues can populate said arbitrarily bent backbone so that this "designable protein backbone configuration" is in low energy stae condition and is thus "designable". Such configuration might be "designable", but there is no connection of such "designable" configuration to any "real world" utility (e.g., a pharmaceutical utility). Furthermore, there are no specific examples of the claimed design method present in the specification that would attest to any utility of the method.

Examiner maintains that the specification does not relate to any "real world" substantial utility of the claimed method and that further research is needed to identify the immediate benefit to the public from using the method. In this regard Examiner maintains that the reference of Shakhnovitch et al is relevant:

> "Most of the present experimental [protein design] approaches enjoyed only limited success, providing polypeptides that in most cases fold into compact but mostly disordered conformations of molten-globule-like species. It is quite possible that limitations in experimental design result from a relatively low synergism between experiment and theory."
>
> p. R45, right column.

Identifying use of the claimed method of polypeptide design would require carrying out further research. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. "An application must show that an invention is useful to the public as disclosed in its current form, not that it may be useful at some future date after further research. To satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public". (*In re Fisher,* U.S. Court of Appeals for the Federal Circuit, 04-1465 (Serial No. 09/619,643), September 7, 2005).

Consequently, the claimed subject matter is not supported by substantial or well established utility.

Response to arguments

Applicant first clarifies that "the products of the method of the present invention is not a polypeptide with specific amino acid sequences but are designable configurations which constitute desirable new folds that can be utilized in the production of new and useful proteins" (p. 20). This is exactly one of the reasons why the utility rejection has been applied. The method begins from a random protein backbone populated with model spheres or space-filling generic side chains, from configurations of which random sequences of hydrophobicities are generated which leads to identification of a subpopulation of configurations of said protein backbone populated with model spheres or space-filling generic side chains which are "designable" and although are novel and previously unknown, can, potentially, be utilized in the production of new and useful proteins. Examiner maintains that such method the specification does not relate to any substantial or "real world" utility of the claimed method and as all the method achieves is bending a model peptide backbone into certain configurations using arbitrary set of angles and model residues, further research is needed to identify the immediate benefit to the public from using such method.

Applicant further argues that the "real world" utility of the method is in eliminating undesirable configurations. Examiner disagrees that this attests to a "real world" utility. Again, neither eliminating undesirable configurations, nor producing a subpopulation of abstract backbone configurations produces an immediate benefit to the public which can be achieved without a further research.

Applicant directs attention to page 4, lines 12-19, 29-31, as providing evidence for both specific and substantial utility. The first section however, provides definition of a "designable" configuration for an "unusually large number of amino acid sequences". The instant claims, however, are directed neither to "unusually large number of sequences", nor to "amino acid sequences". The subsequent part of p. 4 addresses uses of peptides and proteins in general, which does not provide a sufficient nexus to use of a subpopulation of configurations of random protein backbones populated with model spheres or space-filling generic side chains.

Further, applicant again reiterates that the claims are directed not to a product requiring research but to a computer-implemented design method. A computer-implemented design method. However, in the absence of utility for the products generated by the method (which products undoubtedly require further research for their use), the method does not provide any other practical utility providing an immediate benefit to public. It might be speculated that use of the method might, in future, produce a useful result, such as "to predict the folding of natural proteins"; however, such result is clearly not achievable by the instant method, and would require further research to be attempted to be obtained. All that current method achieves is identifying a subpopulation of model configurations that itself have no specific or substantial utility (*cf.* MPEP 2707.01.1.(C)).

With respect to Shakhnovitch reference, applicant argues that despite the statement about the lack of success in experimental protein design, the reference also describes a "success story based on synergism of theory and experiment". Examiner

maintains that the instant method is rather in the realm of theory and further experimentation is needed to prove its practical utility.

Applicant further provides a lengthy citation from Guidelines on Utility without pointing out at a source of disagreement or argument. Examiner fully agrees with the guidelines in that a deficiency under the "useful invention" requirement occur when an applicant "fails to identify any specific and substantial utility", or "makes its usefulness immediately apparent to those familiar with the technological field of the invention." This, and the need for conducting further research to demonstrate substantial utility of the invention, were the reasons for applying the rejection.

With respect to Wingreen Declaration, applicant argues that the Declaration demonstrates the utility of the method in that it had led to a protein which had folding properties that were on par with natural proteins. Examiner disagrees that to be capable to fold, which is a normal property of protein structures, provides a proof of any specific or substantial utility. It is equivalent to demonstrating any other physico-chemical property characteristic for proteins, e.g., ability to melt or have a taste. As stated in the rejection above, the claimed method operates abstract, non real-world, model protein backbones populated with model spheres, and abstract sequences of hydrophobicities; wherein the method at the end arrives at previously unknown protein structures which do not have either a specific or substantial utility.

8. Claims 22-26,28,29,31-33,35-40 are also rejected under 35 U.S.C. §112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Claim Rejections - 35 U.S.C. § 101 (non-statutory invention)

9. Claims 22-26,28,29,31-33,35-40 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The rejection is revised in more details in view of recently released "Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility"[1]. The following analysis of facts of this particular patent application follows the analysis suggested in the "Guidelines". Note that the text of the Guidelines is italicized.

Section 101 of title 35, United States Code, provides:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

To satisfy section 101 requirements, the claim must be for a practical application of the § 101 judicial exception, which can be identified in various ways (Guidelines, p. 19):

- The claimed invention "transforms" an article or physical object to a different state or thing.

- The claimed invention otherwise produces a useful, concrete and tangible result, based on the factors discussed below.

[1] Available at http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/guidelines101_20051026.pdf

In the instant case, the claimed invention does not "transform" an article or physical object to a different state or thing. This does not preclude the subject matter to be patentable as, for eligibility analysis, as

physical transformation "is not an invariable requirement, but merely one example of how a mathematical algorithm [or law of nature] may bring about a useful application." AT&T, 172 F.3d at 1358-59, 50 USPQ2d at 1452. If the examiner determines that the claim does not entail the transformation of an article, then the examiner shall review the claim to determine if the claim provides a practical application that produces a useful, tangible and concrete result. In determining whether the claim is for a "practical application," the focus is not on whether the steps taken to achieve a particular result are useful, tangible and concrete, but rather that the final result achieved by the claimed invention is "useful, tangible and concrete." The claim must be examined to see if it includes anything more than a § 101 judicial exception. If the claim is directed to a practical application of the § 101 judicial exception producing a result tied to the physical world that does not preempt the judicial exception, then the claim meets the statutory requirement of 35 U.S.C. § 101. If the examiner does not find such a practical application, the examiner has determined that the claim is nonstatutory. (Guidelines, p. 20)

In the instant case, the question is thus whether the final result achieved by the claimed invention .produces a result which satisfies all three criteria of being useful, and concrete, and tangible.

*(1) **"USEFUL RESULT"** For an invention to be "useful" it must satisfy the utility requirement of section 101, i.e., it has to be (i) specific, (ii) substantial and (iii) credible.*

As discussed in the utility rejection above, the invention does not satisfy the criteria of utility requirements as not being specific and substantial.

When the examiner has reason to believe that the claim is not for a practical application that produces a useful result, the claim should be rejected, thus requiring the

applicant to distinguish the claim from the three § 101 judicial exceptions to patentable subject matter by specifically reciting in the claim the practical application. In such cases, statements in the specification describing a practical application may not be sufficient to satisfy the requirements for section 101 with respect to the claimed invention. Guidelines, p. 21.

In the instant case, while specification addresses some general utilities of proteins and peptides, there is no recitation of a practical application in the claim.

If the specification discloses a practical application of a § 101 judicial exception, but the claim is broader than the disclosure such that it does not require a practical application, then the claim must be rejected. Guidelines, p. 21:

In the instant case, the claims are directed to computational method of generating previously unknown protein backbone configurations and populating them with amino acid residues. Such method does not require any practical application of thus designed proteins having no particular utility.

*(2) **"TANGIBLE RESULT"** The tangible requirement does not necessarily mean that a claim must either be tied to a particular machine or apparatus or must operate to change articles or materials to a different state or thing. However, the tangible requirement does require that the claim must recite more than a § 101 judicial exception, in that the process claim must set forth a practical application of that § 101 judicial exception to produce a real-world result. The opposite meaning of "tangible" is "abstract."*

In the instant case, the claimed invention is directed to an abstract method which operates abstract, non real-world, model protein backbones populated with model spheres, and to abstract sequences of hydrophobicities; wherein the method at the end

arrives at previously unknown designed proteins which do not have a demonstrated real-world utility.

*(3) **"CONCRETE RESULT"** Usually, this question arises when a result cannot be assured. In other words, the process must have a result that can be substantially repeatable or the process must substantially produce the same result again. The opposite of "concrete" is unrepeatable or unpredictable.*

In the instant case, the method seems to be concrete in that, for a given set of dihedral angles and for given set of backbone configurations of a pre-selected length, it would produce a reproducible number of final configurations. However, as the claims do not specify which set of dihedral angles is to be used and for which of the unlimited number of protein configurations of a given length, the method is unlikely to produce the same result again. Also, the method is unlikely to produce the same result again, as selecting configurations which are not only designable but also novel is unrepeatable, because it is unpredictable and unrepeatable which sequences will be considered as "novel" at any given time.

Thus, the final result achieved by the claimed invention .produces a result which does not satisfy all three criteria of being useful, and concrete, and tangible.

Response to arguments

Applicant argues that the claimed method is designed to "design and produce polypeptides with great, evident potential for use in real world". Examiner failed to find a proof for a "great, evident potential for use in real world" (see utility rejection).

Further, applicant argues that the method allows "immediate elimination of myriad undesirable possibilities". Had the method had produced a practical result, e.g., a protein with improved and desirable characteristics, elimination of undesirable possibilities would be indeed considered as a practical result. In the instant case, however, the method produces a new protein fold populated with random residues; which is a result not satisfying the criteria of being useful, concrete, and tangible.

With respect to Wingreen Declaration, applicant argues that the Declaration demonstrates "tangibility" of the invention as it "demonstrates the design and production of a polypeptide with folding properties that are on par with natural proteins". It is not clear to Examiner what relation to tangibility has the ability to have ability to fold which is an inherent property of all proteins. As stated in the rejection above, the claimed method operates abstract, non real-world, model protein backbones populated with model spheres, and abstract sequences of hydrophobicities; wherein the method at the end arrives at previously unknown designed proteins which do not have a demonstrated real-world utility. Having a physico-chemical characteristic – folding – known for proteins in general, does not amount to a practical utility.

Conclusion.

10. No claims are allowed.

11.**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael Borin, Ph.D.
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Art Unit 1631

mlb
11/18/2005